Pathologic Complete Response to Neoadjuvant Crizotinib in a Lung Adenocarcinoma Patient With a *MET* Exon 14 Skipping Mutation

Julia K. Rotow,[1,2] Gavitt A. Woodard,[3] Anatoly Urisman,[4] Caroline E. McCoach,[1,2] Trever G. Bivona,[1,2] Brett M. Elicker,[5] David M. Jablons,[3] Collin M. Blakely[1,2]

Clinical Practice Points

- Hepatocyte growth factor receptor (*MET*) exon 14 (*METex14*) skipping mutations are an emerging therapeutic target in non–small-cell lung cancer.
- Neoadjuvant treatment with the MET tyrosine kinase inhibitor crizotinib in a locally advanced, unresectable *METex14*-mutated lung adenocarcinoma led to conversion to resectable status with pathologic complete response.
- Neoadjuvant treatment with targeted therapies might provide an alternative to neoadjuvant chemotherapy for patients with oncogenic driver mutations.

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Introduction

Neoadjuvant chemotherapy is a standard of care option for bulky, but potentially resectable, non–small-cell lung cancers (NSCLCs).[1] Although major pathologic response (<10% viable tumor cells) and pathologic complete response (pCR) to neoadjuvant chemotherapy are uncommon they are associated with improved overall survival.[2] It is unknown whether neoadjuvant treatment with a targeted therapy can lead to similar or improved outcomes, potentially with reduced toxicity. Hepatocyte growth factor receptor (*MET*) exon 14 skipping (*METex14*) mutations predict response to MET tyrosine kinase inhibitors (TKIs) in the metastatic disease setting.[3] Herein, we describe a patient with locally-advanced *METex14*-mutated lung adenocarcinoma who experienced dramatic clinical benefit and pCR after neoadjuvant treatment with crizotinib.

Case

A 59-year-old Asian woman presented with cough and chest pain, and was found to have an unresectable 15-cm right upper lobe lung mass with multiple enlarged mediastinal lymph nodes and tiny right-sided pleural nodules of uncertain significance (Figure 1). An endobronchial ultrasound-guided fine needle aspiration of a station 4R lymph node showed lung adenocarcinoma (Figure 2A). Clinical next-generation sequencing of tumor tissue (FoundationOne, Foundation Medicine, Cambridge, MA) and plasma cell-free DNA (Guardant360, Guardant Health Inc, Redwood City, CA) identified a *METex14* mutation (Figure 1).

The patient was treated with the MET TKI crizotinib (250 mg twice daily), which resulted in a 60% decrease in size of the primary right upper lobe lesion and resolution of previously identified small right pleural nodules in computed tomography (CT) chest imaging that was obtained after 2 months of treatment. Hypermetabolism of the primary lesion was reduced and there was resolution of hypermetabolic mediastinal lymph adenopathy on subsequent fluorine-18 fluorodeoxyglucose (F18-FDG) positron emission tomography (PET)/CT at 18 weeks of treatment (Figure 1). A biopsy of the residual right upper lobe lesion at 3 months of treatment showed only necrotic debris and the *METex14* mutation was no longer detectable in plasma.

After 8 months of crizotinib treatment with sustained radiologic response the patient underwent a right-sided pneumonectomy with mediastinal lymph node dissection for resection of her residual right lung mass. Pathology review of her pneumonectomy specimen showed fibrosis and macrophage accumulation with only necrotic, nonviable tumor cells identified, consistent with pCR (Figure 2B). She recovered well postoperatively without significant functional limitations and resumed crizotinib treatment 1 week postoperatively

[1]Department of Medicine
[2]Hellen Diller Family Comprehensive Cancer Center
[3]Department of Surgery
[4]Department of Pathology
[5]Department of Radiology, University of California, San Francisco, San Francisco, CA

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Address for correspondence: Collin M. Blakely, MD, PhD, 550 16th St, Box 3211, San Francisco, CA 94158
E-mail contact: Collin.blakely@ucsf.edu

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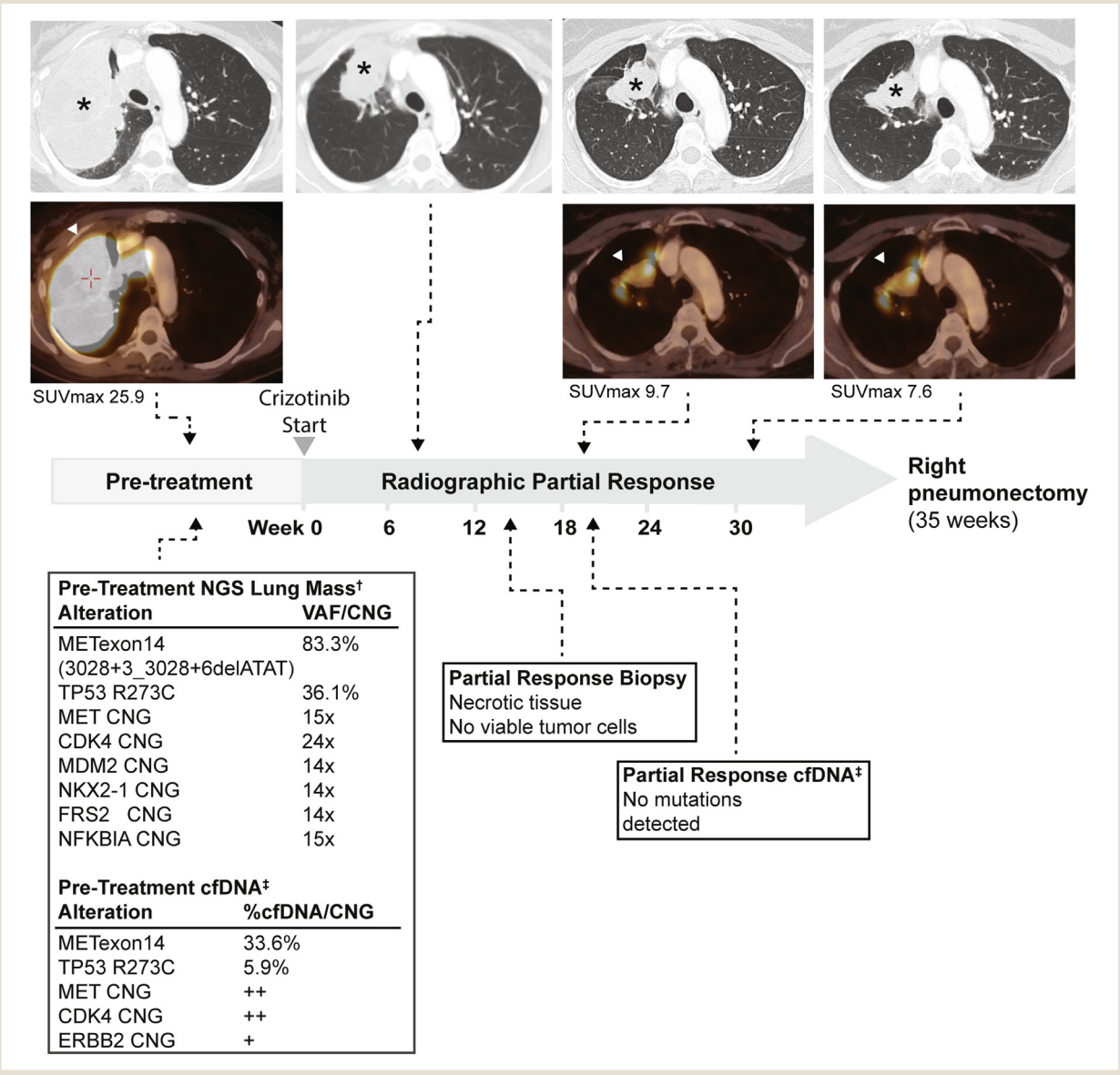
Figure 1 Radiographic and Molecular Response to Neoadjuvant Crizotinib. Initial Computed Tomography Imaging Showed a Large Right Upper Lobe Lung Mass (White Arrowhead/Black Asterisk) With Mediastinal Lymphadenopathy. Serial Imaging Showed Partial Radiologic Response (62% Reduction According to Response Evaluation Criteria in Solid Tumors 1.1) After Treatment With Crizotinib. SUVmax Describes Maximal Standardized Uptake Value (SUV) in the Dominant Right Upper Lobe Lung Lesion. Initial Clinical Sequencing of Her Right Lung Tumor Tissue (†FoundationOne, Foundation Medicine, Cambridge, MA) and of Plasma Cell-Free DNA (cfDNA;‡Guardant360, Guardant Health Inc, Redwood City, CA) Showed a *MET* Exon 14 Skipping Mutation. A Repeat Right Lung Tumor Biopsy After 3 Months of Treatment Showed Only Necrotic Tissue and a Repeat Plasma cfDNA After Approximately 4 Months of Treatment Did Not Detect Any Mutations. The Patient Ultimately Underwent a Right Pneumonectomy to Resect Her Residual Right-Sided Lung Mass After 8 Months of Therapy



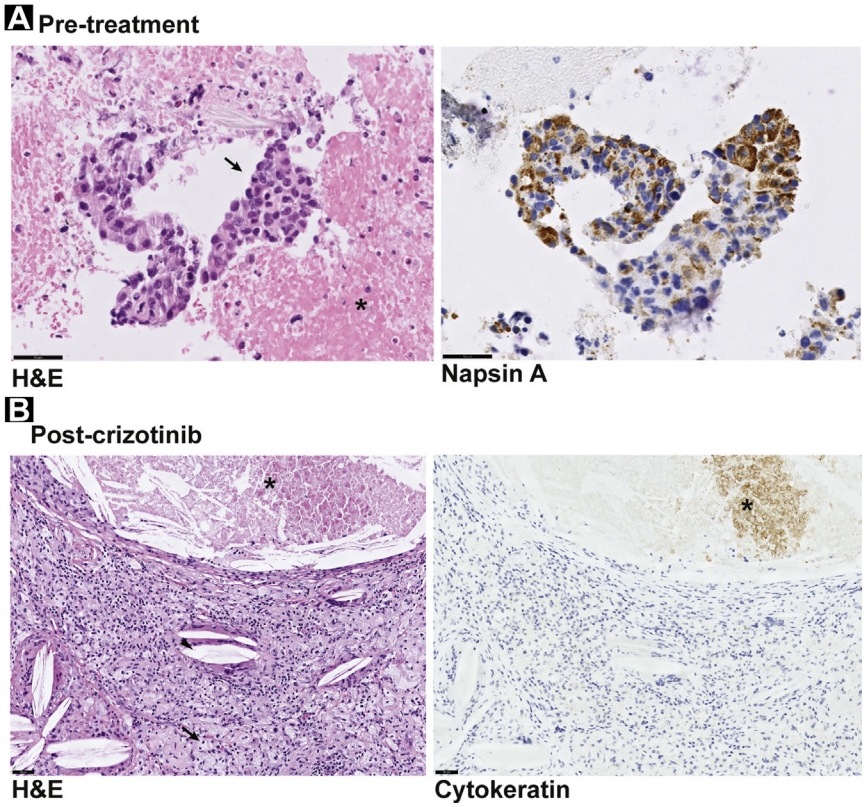
Abbreviations: Amp = amplification; CNG = copy number gain; VAF = variant allele fraction

with good tolerance to therapy. There was no evidence of recurrent disease at 6 months of follow-up after surgery.

Discussion

Neoadjuvant chemotherapy plays an established role within the standard of care for locally advanced NSCLC, offering the potential to convert borderline resectable to resectable disease and to limit the morbidity of definitive local therapy. A meta-analysis showed improvement in 5-year overall survival (45% vs. 40%) for patients with resectable stage IB/IIIA disease who received neoadjuvant therapy.[4] Although this overall improvement in survival is of limited magnitude, the presence of a major pathological response to

Figure 2 Pathologic Complete Response After Crizotinib Treatment. (A) Pretreatment Endobronchial Ultrasound-Guided Fine-Needle Aspiration of the Right Level 4 Mediastinal Lymph Node Shows Poorly Differentiated Adenocarcinoma (Black Arrow) With Abundant Necrosis (*). Hematoxylin and Eosin (H&E) and Napsin A Immunohistochemistry; Bar = 50 μm. (B) Right Pneumonectomy Specimen After Neoadjuvant Crizotinib Shows Replacement of the Tumor by Fibrosis With Prominent Accumulation of Foamy Macrophages (Black Arrow), Cholesterol Debris (Black Arrowhead), and Cyst-Like Areas of Necrosis With Tumor Cell Ghosts, Which Still Retain Keratin Staining (*), But No Viable Tumor Is Identified. H&E, Bar = 50 μm; Cytokeratin AE1/AE3 Cam5.2 Immunohistochemistry, Bar = 200 μm



neoadjuvant chemotherapy, defined as <10% viable tumor cells on pathology review of the resection specimen, is strongly predictive for improved overall survival (85% vs. 40% 5-year overall survival; $P < .0001$).[5]

The role of neoadjuvant targeted therapy or immunotherapy in NSCLC is less well established. Early reports describing the use of these classes of therapy in the neoadjuvant setting, measured according to pathologic response rates, suggest potential for clinical benefit as well as acceptable safety profiles. In a series of 7 patients with operable epidermal growth factor receptor (*EGFR*)-mutated NSCLC treated with a neoadjuvant EGFR TKI, <50% residual viable tumor was seen in 3 patients, in 2 of whom there was <5% viable tumor.[6] A near-complete response to neoadjuvant crizotinib was reported in a patient with anaplastic lymphoma kinase (*ALK*)-rearranged NSCLC after disease progression during an initial trial of neoadjuvant platinum-based chemotherapy.[7] The neoadjuvant role of immunotherapy has also been evaluated. In a pilot study of 21 patients a major pathologic response rate was seen in 45% of patients treated with neoadjuvant nivolumab. As described in this case, the radiographic response rate (10% partial radiographic response) underestimated the pathologic response rate.[6] A similar discordance between radiographic response rates (0% overall response rate according to Response Evaluation Criteria in Solid Tumors criteria) and pathologic response rates (21% major pathologic response rate) was seen in a study that evaluated the use of neoadjuvant atezolizumab in patients with resectable NSCLC.[8]

For metastatic NSCLC response rates to targeted therapy are higher than those seen with first-line platinum-based chemotherapy, and associated with improved overall survival.[9] In the neoadjuvant setting, radiographic response rates of 35.4% and 53.3%, and pCR rates of 4% and 10.5% have been reported to gemcitabine/cisplatin and carboplatin/paclitaxel, respectively.[10,11] In comparison, radiographic response rates of 80% and higher have been reported to first-line treatment with the EGFR and ALK TKIs osimertinib and alectinib in the setting of *EGFR*-mutated or *ALK*-rearranged metastatic disease.[12,13] Although there is currently no US Food and Drug Administration-approved MET TKI for use in *METex14*-mutated NSCLC, an unconfirmed response rate of up to 44% has been reported in an earlier-phase study.[14] Multiple ongoing clinical trials are evaluating novel MET TKIs for use in *METex14*-mutated

Table 1 Selected Clinical Trials That Evaluated Neoadjuvant Targeted Therapy or Immunotherapy in NSCLC

Patient Population	Treatment	ClinicalTrials.gov
***EGFR*-Mutated NSCLC**		
Stage II-IIIA, resectable	Erlotinib	NCT01470716
Stage III, unresectable	Gefitinib	NCT02347839
Stage II-IIIA, resectable	Gefitinib	NCT03203590
Stage IIIA/B	Osimertinib	NCT02824952
Stage I-IIIA, resectable	Osimertinib	NCT03433469
NSCLC With *ALK*, *ROS1*, or *METex14* Alterations		
Stage IA-IIIA, resectable	Crizotinib	NCT03088930
Neoadjuvant Checkpoint Inhibitor Therapy		
Stage II/IIIA, resectable	Pembrolizumab	NCT03197467
Stage IB-IIIA, resectable	Pembrolizumab	NCT02818920
Stage IB-IIIA, resectable	Atezolizumab	NCT02927301
Stage IB-II	Durvalumab	NCT03030131
Stage I-IIIA, resectable	Pembrolizumab with radiation	NCT03217071
Stage IIIA, resectable	Chemoradiation with pembrolizumab	NCT02987998
Stage IB-IIIA, resectable	Nivolumab with or without Ipilimumab	NCT02259621
Stage IIIA, resectable	Durvalumab with or without tremelimumab with radiation	NCT03237377
Stage IIB/IIIA, resectable	Platinum-based chemotherapy with pembrolizumab	NCT03425643
Stage II-IIIB, resectable	Platinum-based chemotherapy with or without atezolizumab	NCT03456063
Stage IIIA, resectable	Platinum-based chemotherapy with nivolumab	NCT03081689

Abbreviation: NSCLC = non–small-cell lung cancer.

or *MET*-amplified NSCLC, including tepotinib,[15] capmatinib,[16] merestinib (NCT02920996), and savolitinib (NCT02897479). In combination with a favorable side effect profile, neoadjuvant targeted therapy might be a reasonable option for patients with lung cancers that harbor a targetable oncogene, with lower predicted toxicity and higher response rates than the platinum-based chemotherapy typically used for neoadjuvant therapy.

Conclusion

The response to neoadjuvant crizotinib in *MET* exon 14-mutated NSCLC described herein converted an unresectable tumor to one in which a complete R0 resection was possible. Importantly, the surgical pathology showed complete pathological response (Figure 2) despite persistent residual right lung mass hypermetabolism on F18-FDG PET/CT imaging. This pattern mirrors findings from recent studies of neoadjuvant checkpoint inhibitors,[6,8] in which the degree of radiographic response underestimated pathologic response rates.

The case highlights the need for prospective studies to evaluate the role of precision medicine-based, molecularly targeted anticancer therapies in the neoadjuvant setting.[17] Such prospective studies are the subject of ongoing clinical trials (Table 1), including those evaluating osimertinib (NCT03433469) and crizotinib (NCT03088930) in *EGFR*-mutated and *MET*/*ALK*/ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*)-altered, surgically resectable NSCLC.

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Disclosure

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